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(57) Abstract

The present invention relates to inhalable drugs in particulate form. More specifically, the present invention is directed to an excipient powder that comprises a coarse first fraction having a particle size of 10μm, a fine second fraction having a particle size of no more than 10μm and a third fraction consisting of ternary agents. The excipient powder has been found to be beneficial in the administration of phamarceuticals to the pulmonary system.

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INHALATION POWDERS

This invention relates to inhalable drugs in particulate form and the use thereof. Particularly, it is concerned with excipient powders which are mixed with such drugs to facilitate handling and metering, and maximising the delivery of inspired drug to target sites in the lungs.

Inhalable drugs are typically provided in micronised form with average particle sizes of up to 10 μm. The particulate drug is mixed with an excipient powder of larger average particle size, and the drug particles become attached to the excipient or carrier particles to create a generally homogeneous mixture. The larger particle size of the excipient results in the powder mixture being flowable, and the homogeneity of the mixture enables it to be metered into accurately measurable doses. This is of particular importance when only very small quantities of the drug are required in a dose. Dilution of the drug in the excipient does, of course, facilitate accurate metering. Excipient powders of this kind and pharmaceutical powder compositions for inhalation utilising such excipients are described in British Patent Specification No. 1,242,211.

When an inhalation powder of the kind referred to above is inspired, the drug particles detach themselves from the larger carrier particles which, by virtue of their own momentum, are effectively separated from the inflowing air. The smaller drug particles remain in train, and are carried to the lungs.

Effective particle sizes for the excipient or carrier powder has been the subject of considerable research. In his Thesis No. DX 187842 published at the University of London Library in August 1991, Nuha M. Kassem examines the effect of using different sized excipients on the extent to which a drug carried thereby penetrates the lungs, and thereby reaches the target sites. He conducted experiments using a multi-stage impinger to simulate the inhalation process, with different sizes of carrier particles, ranging from below 10μm to over 180μm. He also included an experiment using an excipient powder in which the particle size was not predetermined, but rather broad and comprised of particles below 10μm and up to and over 80μm, reaching the conclusion that the performance of this unclassified powder combines the performance of different ranges of particle sizes inherent in such a powder.

In their European Patent Specification No. 0,663,815 Boehringer Ingelheim International GmbH describe an excipient powder for use with an inhalable micronised drug which has coarser and finer fractions. The coarser fraction has an average particle size of at least 20μm. The finer fraction has an average particle size of no more than 10μm. By specifically including a finer fraction in the excipient powder, it is stated that the amount of drug that reaches the lungs can be controlled, without losing the benefits that are afforded by the use of the larger excipient particles, particularly the flowability of the mixture of excipient and inhalable drug, and the metering of doses therefrom.

We have found that the performance of inhalable pharmaceutical powder compositions can be further enhanced by the careful selection of coarse and fine

fractions in the excipient powder, and by the use of a ternary particulate agent in the mixture. Firstly, we have found that some benefits can be achieved by excluding from the excipient mixture particles having an intermediate size, i.e., neither coarse nor fine. For example, coarse particles of at least 30μm, preferably at least 50μm, have a clearly beneficial effect on handleability of the powder mixture, and fine particles of no more than 10μm are effective in enhancing the delivery of drug to target sites in the lungs. The intermediate sized particles, between 10 and 30μm (preferably 10μm to 50μm), tend to have an adverse affect on handleability without imparting any benefit to the drug delivery characteristics. Thus, an excipient powder consisting of two discrete fractions, and excluding particles of intermediate size, can offer considerably improved performance in combination with a particulate, normally micronised, drug. It will, though, be appreciated that it may be impossible to wholly exclude intermediate sized particles from the excipient mixture; the benefits of this aspect of the invention will also be apparent even when the proportion of intermediate sized particles is substantially reduced.

A typical excipient powder according to the invention comprises a coarse first fraction of which at least 80% by weight has a particle size of at least 10μm; a fine second fraction of which at least 90% by weight has a particle size of nor more than 10μm; and a third fraction consisting of a ternary agent. Preferably, no more than 15%, and most preferably no more than 10% by weight of the coarse fraction has a particle size of less than 10μm.

The preparation of powder fractions with the requisite particle size ranges can be accomplished by sieving out the particles to be included or mixing pre-classified powders; i.e., powders in which the particle size range is already accurately defined. Mixing will normally be by high sheer blending. Pre-classified coarse powders are available as staple products, for example a lactose powder of which at least 80% by weight has a particle size of at least 50μm is available under the Trade Mark Meggle Spherolac 100.

Effectively pre-classified fine powder fractions can be prepared by micronisation or spray drying. In all embodiments of the invention the fine fraction and, where used, the ternary agent, will be provided in the smallest possible particle sizes.

In a second aspect, we have found that the use of a ternary agent can also enhance the delivery of particulate drug to target sites in the lungs. Such a ternary agent would be provided in particulate form as an additional fine fraction, but slightly larger particle sizes are acceptable. Suitable ternary agents include a wide range of water-soluble and physiologically acceptable materials, but will normally be water surface active agents or amino acids, peptides and polypeptides or derivatives thereof. A particularly preferred ternary agent is L-leucine.

Typical carrier powders embodying the invention, excluding drug or any ternary agent, have the following particle size analysis by weight:

Size BanD (μm)	<10	10-30	30-50	10-50	50-100	>100	Total
I	18.62	3.25	3.31	6.55	27.14	47.69	100
II	27.58	2.95	2.94	5.39	24.09	42.44	100
III	36.55	2.65	2.56	5.21	21.04	37.2	100

The particle size distribution in powders useful in the practice of the invention can be established using a Malvern Mastersizer, a proprietary product available from Malvern Instruments Limited, Malvern, U.K.

Additional components, such as flavour-enhancers and anti-oxidants, can be included in powders according to the invention. Primarily, such additional components would have the purpose of rendering the powder and drug mixture more palatable, and/or more stable.

A typical excipient powder according to the invention for use with an inhalable particulate drug comprises a coarse first fraction of which at least 90% by weight has a particle size of at least 10μm and/or at least 80% by weight has a particle size of at least 50μm; a fine second fraction of which at least 90% by weight has a particle size of no more than 10μm; and a third fraction consisting of a ternary agent of which typically at least 90% by weight has a particle size of no more than 20μm. The first and second fractions will often consist of the same material, such as sugar, e.g., mono, di, or polysaacharide, typically lactose. The proportions by weight of the first fraction to the second fraction will normally be in the range 50:1 to 2:1, preferably 20:1 to 3:1, and most preferably 10:1 to 4:1. The ratio by weight of the first and second fractions to the third fraction is normally in the range 1000:1 to 10:1, typically 400:1 to 25:1 and preferably 200:1 to 50:1.

The amount of drug included in an inhalable pharmaceutical composition of the kind to which the invention relates is normally relatively small. Typically the ratio by weight of excipient powder to drug is as high as 1000:1. However, certain drugs can be used in much larger quantities in excipients according to the invention, and the ratio of excipient to drug can be as low as 1:1. Preferred ratios are in the range 500:1 to 3:1, with the most preferred ratios being in the range 200:1 to 10:1.

We have conducted some preliminary tests of formulations embodying the invention using an Astra Draco Multi-Stage Liquid Impinger (MSLI). The coarse lactose fraction in each case is Meggle SpheroLac 100. The fine fractions and L-leucine are prepared by micronisation. The results thereof are set out below.

<u>Example 1</u>

Two carrier formulations were prepared as follows:

Formulation A:

Coarse lactose	(>80% by mass over 50µm in size) =	89.0%
Fine lactose	(>90% by mass below 10µm in size) =	10.0%
Fine L-leucine	(>90% by mass below 10µm in size) =	1.0%

Formulation B:

Coarse lactose	(>80% by mass over 50µm in size) =	90.0%
Fine lactose	(>90% by mass below 10µm in size) =	10.0%

The carrier formulations were each blended with 2% of a corticosteroid, commonly used for the prophylactic treatment of asthma, in a high-shear blender.

A small sample of each drug blend was then filled into a separate reservoir-type inhaler device and its aerosol performance assessed using the MSLI.

The mean RF (Respirable Fraction) from three determinations using the drug blend containing ternary agent was approximately 60%, compared to a value of only approximately 40% for the formulation without L-leucine.

Example 2

Two carrier formulations were prepared as follows:

Formulation A:

Coarse lactose	(>80% by mass over 50μm in size)	=	78.0%
Fine lactose	(>90% by mass below 10μm in size)	=	20.0%
Fine L-leucine	(>90% by mass below 10μm in size)	=	2.0%

Formulation B:

Coarse lactose	(>80% by mass over 50μm in size)	=	79.0%
Fine lactose	(>90% by mass below 10μm in size)	=	20.0%
Fine L-leucine	(>90% by mass below 10μm in size)	=	1.0%

The carrier formulations were each blended with 1.5% of a corticosteroid in a high-shear blender.

A small sample of each drug blend was then filled into a separate reservoir-type inhaler device and its aerosol performance assessed using the MSLI.

The mean RF (from three determinations) using the drug blend containing 2% ternary agent was approximately 67%, compared to a value of only 63% for the formulation with 1% L-leucine.

The respirable fraction (RF) was calculated at a flow rate of 60 litres per minute by dividing the fine particle dose or amount of drug found in the lower stages in the impinger, by the emitted dose or total mass of drug recovered from the impinger as a whole. Example 1 demonstrates the considerable improvement in the

respirable fraction achieved by the use of the specified ternary agent. Example 2 shows that this benefit is enhanced by the use of additional amounts of the ternary agent.

CLAIMS:

1. An excipient powder for inhalable drugs comprising a coarse first fraction of which at least 80% by weight has a particle size of at least 10μm; a fine second fraction of which at least 90% by weight has a particle size of no more than 10μm; and a third fraction consisting of a ternary agent.

2. An excipient powder according to Claim 1 wherein at least 90% by weight of the ternary agent has a particle size of no more than 20μm.

3. An excipient powder according to Claim 1 or Claim 2 wherein at least 80% by weight of the coarse fraction has a particle size of at least 50μm.

4. An excipient powder according to any preceding claim wherein the first and second fractions consist of the same material.

5. An excipient powder according to claim 4 wherein the material is lactose.

6. An excipient powder according to any preceding claim wherein the ratio by weight of the first fraction to the second fraction is in the range 50:1 to 2:1, preferably 20:1 to 3:1; and most preferably 10:1 to 4:1.

7. An excipient powder according to any preceding claim wherein the ratio by weight of the first and second fractions to the third fraction is in the range 1000:1 to 10:1; preferably 400:1 to 25:1; and most preferably 200:1 to 50:1.

8. An excipient powder according to any preceding claim wherein the ternary agent is a water-soluble surface active agent.

9. An excipient powder according to Claim 6 wherein the ternary agent is selected from Amino acids, peptides and polypeptides and derivatives thereof.

10. An excipient powder according to Claim 7 wherein the ternary agent is L-leucine.

11. An excipient powder according to any preceding claim wherein particles in the size range 10μm to 30μm represent no more than 10% by weight of the total excipient powder.

12. An excipient powder according to any preceding claim wherein particles in the size range 10μm to 50μm represent no more than 10% by weight of the total excipient powder.

13. An excipient powder for inhalable drugs comprising a coarse first fraction of which at least 90% by weight has a particle size of at least 30μm and a fine second fraction of which at least 90% by weight has a particle size of no more than 10μm, and particles in the size range 10μm to 30μm represent no more than 10% by weight of the total excipient powder.

14. An excipient powder for inhalable drugs comprising a coarse first fraction of which at least 80% by weight has a particle size of at least 50μm and a fine second fraction of which at least 90% by weight has a particle size of no more than 10μm, and particles in the size range 10μm to 50μm represent no more than 20% by weight of the total excipient powder.

15. An excipient powder according to Claim 14 wherein particles in the size range 10μm to 50μm represent no more than 10% by weight of the total excipient powder.

16. An excipient powder according to any preceding claim wherein at least 30% by weight of the coarse first fraction has a particle size of at least 100μm.

17. A powder composition for inhalation comprising an excipient according to any preceding claim and a particulate pharmaceutically active substance.

18. A composition according to Claim 16 wherein 90% by weight of the active substance has a particle size of no more than 10μm.